بسم الله الرحمن الرحيم

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LEVEL OF SERUM URIC IN PATIENTS WITH PREECLAMPSIA COMPARED TO CONTROLS

A thesis submitted in partial fulfillment for the requirements of the Degree of MD in Clinical Pathology

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قال تعالى :

" وقضي ربك ألا تعبدوا الا اياه وبالوالدين احسانا - اما يبلغن عندك الكبر أحدهما أوكلاهما فلا تقل لهما أف ولاتنهرهما وقل لهما قولا كريما * واخفض لهما جناح الذل من الرحمة وقل رب ارحمهما كما ربياني صغيرا".

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Dedication

To my parents: to whom I owe everything

To my husband

To my children

To my brothers and sisters

&

To my friends

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Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
CBG	Cortisol Binding Globulin
CT scan	Computed Tomographic Scanning
2.3.DPG	2.3 diphosphoglycerate
FSH	Follicular Stimulating Hormone
GFR	Glomerulor Filtration Rate
GGT	γ-Glutamyl Transpeptidase
hCG	Human Chorionic Gonadotrophin
HDL	High Density Lipoprotein
HPLC	High Performance liquid chromatography
IL-1	Interleuken-I
IVS	Intervillous Space
LDL	Low Density Lipoprotein
LH	Leutenizing Hormone
MHC	Major Histocompxibiliting Antigens
PCO_2	Partial Carbondioxide Pressure
PGI_2	Prostaglandin I_2 (Prostacyclin)
PIH	Pregnancy Induced Hypertension
PO_2	Partial Oxygen Pressure
TBG	Thyroxin Binding Globulin
TXA_2	Thromboxane A_2

Abstract

Preeclampsia is an important cause of both fetal and maternal morbidity and mortality worldwide and in Sudan. Early diagnosis and follow up will significantly improve the outcome of the disease.

Serum uric acid is widely used for diagnosis and follows up of preeclampsia.

This study is conducted to compare serum uric acid in patients with preeclampsia with normal control.

Objective:

The objective of this study is to estimate the serum uric acid in preeclampsia and in normal pregnancy. It aims also to detect if there is any significant difference, and to relate serum uric acid to the severity of the disease.

Materials and Methods:

This is a case-control hospital based study covering 100 (50 case/50 control) pregnant ladies in their third trimester in the unit of obstetric and gynaecology in KTH. The study was conducted in the period from September 2009 to Jan 2010.

Clinical data was obtained from patients through questionnaire. Serum uric acid was analyzed in the laboratory at the same hospital.

Results: the mean serum uric acid of the control group was 4.47 mg/dL. (within the normal range).

The mean for the case group is 7.35 mg/dL (above the normal range). P value = 0.000 statistically is highly significant.

Serum uric acid correlate well with the severity of disease.

Conclusions and Recommendations:

Preeclampsia is associated with rise in serum uric acid level.

The higher the blood pressure in preeclampsia the higher the rise in serum uric acid level.

It is recommended that serum uric acid measurement is included in the follow up of preeclampsia.

Serum uric acid level should be used as a predictive factor for preeclampsia.

مستخلص البحث

تعتبر مقدمة الارجاج (كلبش) سبباً هاماً لاعاقة ووفيات المواليد والامهات عبر العالم وفي السودان ، التشخيص المبكر ومتابعة الحالات تساهم بصورة ملحوظة في تحسين النتائج .

يعتبر قياس حمض اليوريك في مصل الدم من الفحوصات المختبرية الهامة في تشخيص ومتابعة المرض.

تهدف هذه الدرساة لمقارنة مستوي حمض اليوريك في المصل بين نساء مصابات بمقدمة الارجاج (الكلبش) وآخر حوامل سليمات في السودان.

الاهداف:

تهدف هذه الدراسة لمعرفة مستوي حمض اليوريك في مصل الدم في حالة الحمل السليم ومعرفة مستواه في مصل النساء المصابات ، وتهدف ايضاً لمعرفة اذا ما كان هناك علاقة بين ارتفاع مستوي الحمض في الدم ودرجة اشتداد المرض .

المواد والوسائل:

تمت هذه الدراسة بالمستشفي بمقارنة عينات المرضي بعينات ضابطة . اجريت علي نساء في الثلث الاخير للحمل بقسم النساء والتوليد بمستشفي الخرطوم التعليمي .

تضمنت الدراسة 100 سيدة (50 عينة مصابة و 50 عينة ضابطة) . تم جمع المعلومات السريرية من النساء بواسطة الاستبيان ، تم تحليل حمض اليوريك في مصل الدم في وحدة الابحاث والمعامل في ذات المستشفي .

النتائج:

توصلت الدراسة الي ان متوسط مستوي حمض اليوريك في مصل النساء السليمات (العينة الضابطة) 4.47 ملجم /دس ويعتبر هذا ضمن المعدل الطبيعي ، وفي النساء المصابات 7.35 ملجم/دس وهي اعلي من المعدل الطبيعي وبالتالي يتميز المرض بارتفاع مستوي الحمض في الدم . وتوصلت الدراسة الي انه كلما ازدادت شدة المرض زاد معدل ارتفاع الحمض في المصل وبالتالي يعتبر ارتفاع الحمض دليلاً علي وخامة المرض.

الخلاصة والتوصيات:

يعتبر حمض اليوريك من الموسمات الهامة لمرض مقدمة الارجاج (الكلبش) ، توصي الدراسة باستعماله في متابعة المرض . كما توصي الدراسة باستعمال حمض اليوريك في المسوحات للاختيار المبكر للحالات المعرضة للاصابة بالمرض.

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CHAPTER ONE

1- INTRODUCTION AND LITERATURE REVIEW

1.1. INTRODUCTION

Preeclampsia, a special entity of hypertensive disorders of pregnancy, is a syndrome of reduced organ perfusion secondary to vasospasm and endothelial dysfunction.[1]

Preeclampsia is diagnosed on the basis of high blood pressure, oedema and proteinuria, other clinical features as headache, epigastric pain support the diagnosis, a further support, to the diagnosis is given by chemical markers of organ and system dysfunction such as elevated levels of serum urea and creatinine, liver enzymes and uric acid.[1]

Preeclampsia is an important cause of both fetal and maternal morbidity and mortality complicating up to 5% of pregnancies. In developed countries as UK where prenatal care is a routine it accounts for 15% of preterm deliveries. Worldwide in settings without good prenatal care as in West Africa preeclampsia increases the risk of fetal death five-folds and kills 50,000 women a year.[2]

The only treatment of preeclampsia is delivery of the fetus and placenta.[1] The difficult decision whether to end pregnancy to save a mother with a preterm baby that is not ready for extrauterine life or to continue pregnancy to give a fetus the benefit of time, but still serious complications for fetus and mother are present. Here comes the role of clinical chemistry laboratory to give accurate results of markers of the severity of the disease along with proper clinical assessment.

The utility of uric acid in preeclampsia is being studied intensively worldwide: Its use as a marker of severity or as a pathogenic factor or its predictive value are widely used.

1.2. LITERATURE REVIEW

1.2.1. Physiological and chemical changes in normal pregnancy:

Pregnancy encompasses the period from conception to birth. During this period the pregnant woman experience major physical, chemical and psychological changes that support maternal adaptations and fetal growth and development as well as prepare the mother for the birth process and transition to parenthood.[3]

Most of the changes encountered during pregnancy are progressive and can be attributed to either the very high circulating concentrations of hormones, e.g. estrogens and progesterone that affect many organs and alter the concentrations of many substances In plasma e.g. carrier proteins or physiological changes of maternal organ systems so as to adapt for the increase demand posed by the requirements of the growing fetus, e.g. changes in cardiovascular and respiratory systems.[4]

1.2.1.1. Volume homeostasis:

One of the most fundamental systemic changes of normal pregnancy is fluid retention which accounts for 8-10 kg of the average maternal weight gain of 11-13 kg.[5] Fluid retention mainly affects plasma volume. This is due to a series of other physiological adaptations notably the increase in cardiac output and in renal blood flow.

The factors contributing to fluid retention are: sodium retention; the marked increase in concentrations of anti-natriuretic hormones such as aldosterone and the 20% decrease in plasma oncotic pressure. The consequences of fluid retention are reducation in haemoglobin concentration, haematocrit and serum albumin concentration, while stroke volume and renal blood flow increase. [5]

1.2.1.2. Blood:

Pregnant women undergo an average increase of about 1250 ml of plasma volume which represents 50% increase. Red cell mass also increases but the rise is influenced by iron supplementation: rise up to 30% in women taking iron supplements and 18% in the absence of

iron. But as red cell mass increases by a smaller amount than plasma volume, a fall in haematocrit and haemoglobin concentrations the so-called physiologic anaemia occurs in normal pregnancy.(6)

An increase in the peripheral white cell count normally occurs in pregnancy with a mean of 9500/mm^3, this is due to increase in neutrophil count which returns to normal 6 weeks postpartum. Eosinophils, lymphocytes and monocytes remain normal. Platelets count drops with a mean of 260.000/mm^3. Circulating levels of coagulation factors VII, X and fibrinogen show dramatic increase, factor II, V & VIII remain unchanged while factors XI and XIII decrease.(6)

Pregnancy is considered as a hypercoagulable state, which is useful at the time of placental separation. At term, about 550 ml of blood flows through the placental bed per minute. Without effective and rapid haemostasis a woman could die from bleeding within a few minutes. The myometrium contraction is the first line of defense compressing the blood vessels supplying the placental bed.

The disadvantage of this hypercoagulable state is the increased risk of thrombosis and thromboembolism[5].

1.2.1.3. Cardiovascular Changes:

When plasma volume expands following fluid retention both heart rate and stroke volume increase by 10-20% and 10% respectively, resulting in increase of 30-50% of cardiac output from 5 L/min before pregnancy to 7 L/min.[5] Despite the increase in circulating plasma volume and cardiac output, the greater part of normal pregnancy is characterized by a reduction in arterial blood pressure.[6]

The decrease in peripheral vascular resistance is a major feature of a normal pregnancy, many factors are involved but it seems that the predominance of vasodilator factors e.g., progresterone and prostaglandins over vasoconstrictor factors and the presence of uteroplacental circulation which functions as a physiologic shut are the most important. [6]

1.2.1.4. Respiratory system:

Pulmonary blood flow increases as a result of the increase in cardiac output. Tidal volume increases so the

lungs function more effectively, facilitating gas transfer, as a consequence, there is drop (15-20%) of PCO_2, and increase in PO_2. During pregnancy there is an increase in 2,3 disphosphoglycerate (2.3 DPG) concentrations within maternal erythrocytes which promotes the release of oxygen from the red cell at lower levels of haemoglobin saturation so both tissues and fetus get maximum oxygen benefit.[6] Dyspnoea a common symptom of pregnancy seems to result from increased tidal volume rather than increase in respiratory rate[3].

1.2.1.5. The Urinary tract and renal function:

During pregnancy kidneys enlarge up to 70% due to increase in both the interstitial space and intravascular volume, dilatation of ureters, and calicies also occur this is explained by the relaxant effect of progesterone. By the third trimester 97% of women show evidence of stasis or hydronephrosis which contributes to urinary tract infection.[5] The renal blood flow increases by 60-75%, which leads to increase in glomerular filtration rate by 50%.

The increase in glomerular filtration rate itself is responsible for the increase in the clearance of a number of substanbces from the blood stream, so plasma levels of these substances reduce, e.g., blood urea nitrogen, serum creatinine and serum uric acid. There is an increase in total protein excretion to 0.3 grams/day in normal pregnancy.[5] Glycosuria is common in pregnancy due to increase in Glomerular filtration rate and decrease in reabsorbtion mechanisms in proximal renal tubules.[6]

1.2.1.6. The digestive system and liver:

Pregnancy is characterized by decreased gastric motility and decreased gastric secretion consistent with the infrequency of peptic ulcer disease and improvement in pre-existing ulcer symptoms. Increased mucus production in response to estrogen and progesterone may also be involved in improving peptic ulcer disease in pregnancy.[6]

Small intestines show decrease in motility and enhanced absorption of calcium and iron. Large intestines changes during pregnancy are associated with decreased motility and enhanced water and sodium absorption both

factors contribute to constipation encountered by many pregnant women.[6]

Liver function changes include a 30% fall in albumin, two to four folds rise in alkaline phosphatase due to placental iso-enzyme. The occasional spider angiomata and palmer erythema are attributed to increased estrogen levels. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and prothrobin time remain unchanged λ-glutamyl transpeptidase GGT levels show variable changes.[4]

1.2.1.7. Endocrinological changes:

Many of the peptides and steroid hormones produced by the endocrine glands in the non-pregnant state are also produced by intrauterine tissues during pregnancy.

Human chorionic gonadotrophin (hCG) is produced by trophoblastic cells and is detectable within the maternal circulation in small quantities within days of implantation, it has a major role during early pregnancy in maintaining the function of the corpus luteum, as placental production of progesterone predominate later in first trimester hCG levels

decline.[7] hCG also suppresses the secretion of both FSH and LH. [6]

Both estrogens and progesterone have effects upon the myometrium (oestrogen encourages cellular hypertrophy, whereas progesterone discourages contraction) together with prolactin they affect breast tissues. It is likely that they exert effects on many other target tissues during pregnancy such as smooth muscles of the vascular tree and the urinary and gastrointestinal tracts.[5]

An insulin-resistant condition similar to that of type II diabetes accompanies normal pregnancy, human placental lactogen hPL, prolactin, cortisol, estrogen and progesterone are all responsible for this hyperglycaemia.[6]

As the synthesis of thyroxin binding globulin increases (TBG) serum levels of total T_3 and T_4 also increase.[6]

About 40% of calcium is bound to albumin and as albumin concentrations decrease during pregnancy, total plasma calcium also decreases. As fetus needs calcium

maternal absorption of calcium increases and excretion decreases.[5]

ACTH levels remain within the normal range glucocorticoids increase since plasma cortisol binding globulin CBG concentrations increase. Circulating concentration of the anti-natriuretic hormones aldosterone and deoxycorticosterone increase up to ten-folds.[5]

1.2.1.8. Plasma lipids:

Plasma trigelyceride, cholesterol, low-density lipoprotein (LDL) and high density lipoprotein (HDL) are all increased.[7]

1.2.2. Hypertensive Disorders Complicating Pregnancy:

1.2.2.1. Overview:

Hypertensive disorders complicating pregnancy are common and form one of the deadly triad, along with hemorrhage and infection, that result in much of the maternal morbidity and mortality related to pregnancy.[8]

Pregnancy- induced hypertension (PIH) occurs in a round 16 – 24% of first pregnancies and 12 – 15% of

subsequent pregnancies. Pre-eclampsia complicates 3-5% of first pregnancies and 1% of subsequent pregnancies.[8] Preeclampsia accounts for around 16% of maternal deaths. Mortality from hypertensive disorders is much higher in developing countries reaching rates of 70 -120 per 100,000. Of maternal deaths in the United Kingdom 40% are associated with eclampsia. Overall perinatal mortality in pre-eclampsia is around 35 per 1000 total births but may reach 160 per 1000 in severe disease. The most important factor determining outcome is gestational age at delivery; survival being < 40% when delivery is indicated before 28 weeks gestation for gestational age (SGA), perinatal mortality is not increased in PIH.[8]

The term pregnancy induced hypertension was and is still widely used to describe any new-onset pregnancy-related hypertension, it was intended to include hypertension without proteinuria, yet it is a potential precursor to preeclampsia or eclampsia which requires proteinuria for diagnosis. [7]

Recently, the working group of the National High Blood Pressure Education Program (2000) USA has proposed a classification system that will help to deal with all the non-uniform and confusing terminology that has long plagued the diagnosis of hypertension in pregnancy.[1]

1.2.2.2. Diagnosis and classification:

1- Gestational hypertension:

- Blood pressure ≥140/90 mmHg for first time during pregnancy.
- No proteinuria.
- Blood pressure return to normal <12 weeks postpartum.
- Final diagnosis made only postpartum.
- May have other signs of preeclampsia, example epigastric discomfort or thrombocytopenia.

2- Preeclampsia:

Minimum criteria:

- Blood pressure ≥140/90 mmHg after 20 weeks gestation. Proteinuria ≥ 300 mg/24 hours or ≥ 1+ dipstick.

Increased certainty of preeclampsia:

- Blood pressure ≥ 160/110 mmHg.
- Proteinuria 2.0 g/24 hours or ≥ 2 + dipstick.
- Serum creatinine > 1.2 mmg/dl unless known to be previously elevated.
- Platelets < 100,000 mm^3.
- Microangiopathic hemolysis that causes increased LDH .
- Elevated ALT or AST.
- Persistent headache or other cerebral or visual disturbances.
- Persistent epigastric pain.

3- Eclampsia: Seizure that can not be attributed to other causes in a woman with pre-eclampsia.

4- Superimposed preeclampsia (on chronic hypertension):

New-onset proteinuria ≥300 mg/24 hours in hypertensive women, but no proteinuria before 20 weeks gestation.

A sudden increase in proteinuria or blood pressure or platelets count <100,000 mm^3 in women with hypertension and proteinuria before 20 weeks gestation.

5- Chronic hypertension:

Blood pressure ≥140/90 mmHg before pregnancy or diagnosed before 20 weeks gestation. Hypertension first diagnosed after 20 weeks gestation and persists after 12 weeks postpartum.(1)

1.2.3. Preeclampsia:

1.2.3.1. Definition:

Preeclampsia is a pregnancy-specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation. Proteinuria is an important sign of preeclampsia the diagnosis is questionable in its absence; proteinuria is described as 300 mg or more of urinary protein per 24 hours or persistent 30 mg/dl (1 dipstick) in random urine samples. The degree of proteinuria may fluctuate widely over any 24 hour period, even in severe cases. Therefore a single random sample may fail to demonstrate significant proteinuria. The more severe the

hypertension and proteinuria the more certain the diagnosis of preeclampsia.[1]

1.2.3.2. Diagnostic feature of preeclampsia:

In addition to hypertension and proteinuria other diagnostic features include: headache, visual disturbances, upper-abdominal pain oliguria, convulsions, elevated serum creatinine, thrombocytopenia liver enzyme elevation, fetal growth restriction and pulmonary oedema. [1]

1.2.3.3. Etiology and risk factors:

In 1916 pre-eclampsia was called the disease of theories almost a century later; this characterization is still accurate. Despite extensive research, the cause of preeclampsia remains uncertain. There are however, well-recognized predisposing factors as primigravid status, family history of preeclampsia or eclampsia, new paternity ,extremes of maternal age (younger than 20 or older than 35 years of age).[9] Pre-existing hypertensive, vascular, autoimmune or renal disease, diabetes mellitus, multiple gestation,nonimmun or alloimune fetal hydrops,hydatidiform mole and obesity.[9]

Data support contribution from several areas in the pathogenesis of the disease: immunogenetic factors, increased vascular reactivity and endothelial injury, coagulation abnormalities, oxygen free radicals and lipid peroxidation, abnormalities of cytotophblastic differentiation and invasion.[9]

1.2.3.4. Pathology of pre-eclampsia:

Pathological deterioration of function in a number of organs and systems, presumably as a consequence of vasospasm and ischaemia, has been identified in severe preeclampsia and eclampsia. The major cause of fetal compromise occurs as a consequence of reduced uteroplacental perfusion.[1]

Cardiovascular changes are basically related to increased cardiac afterload caused by hypertension, hypervolaemia of pregnancy, or iatrogenically by excessive intravenous fluids, and endothelial activation with extravasation into the extracellular space, especially the lungs.[1]

With clinical pre-eclampsia, there is a marked reduction in cardiac output and increased peripheral resistance.(1)

Hemoconcentration is a hallmark of severe preeclampsia and eclampsia. In the late weeks of a normal pregnancy a woman should have a blood volume of nearly 5000 ml compared with about 3500 ml with pre-eclampsia. This is likely a consequence of generalized vasoconstriction made worse by increased vascular permeability.(1)

Some degree of intravascular coagulation is commonly found with pre-eclampsia. (1)

The thrombocytopenia is due to platelet activation and consumption. Its clinical significance is that it reflects the severity of the pathological process in general, the lower the platelet count the greater are maternal and fetal morbidity and mortality.(1)

Thrombocytopenia may be accompanied by evidence of erythrocyte destruction characterized by hemolysis, schizocytosis, spherocytosis, reticulocytosis, hemoglobinuria

and occasionally hemoglobinaemia. These derangements result in part from microangipathic hemolysis.[1]

Plasma levels of rennin, angiotensin II and aldosterone are increased during normal pregnancy, preeclampsia results in a decrease of these hormones toward the normal non-pregnant range. The potent mineralocorticoid deoxycorticosteron (DOC) is increased strikingly in third trimester plasma, it is not reduced by sodium retention or hypertension, this explains why women with preeclampsia retain sodium. Vasopressin levels are normal despite decreased plasma osmolality. Atrial natriuretic peptide is further increased in preeclampsia. [1]

Commonly, the volume of extracellular fluid; manifested as edema, in women with severe preeclampsia has expanded beyond the normally increased volume that characterizes pregnancy. The mechanisms responsible for the pathological expansion is not clear, endothelial injury reduces plasma oncotic pressure displacing intravascular fluid into the surrounding interstitium. Electrolyte

concentrations do not differ appreciably in women with preeclampsia compared with those of normal pregnancy.[1]

During normal pregnancy, renal blood flow and glomerular filtration rate (GFR) increase. Levels that are much below normal non-pregnant values are the consequences of severe preeclambpsia. Plasma uric acid concentrations are typically elevated especially in women with more severe diseases.

In the majority of preeclamptic women GFR, diminished leading to creatinine values twice these of normal pregnancy. In some cases, renal involvement is profound and plasma creatinine may be highly elevated.[1]

There should be some degree of proteinuria to establish the diagnosis of preeclampsia, 24-hour urine excretion should be measured. It was found that urinary dipstick of 1 + proteinuria or greater was predictive of at least 300 mg per 24 hours in 92% of cases.

Albuminuria is an incorrect term to describe proteinuria of preeclampsia, as with any other

glomerulopathy there is increased permeability to most large-molecular-weight proteins.[1]

Liver involvement in preeclampsia- eclampsia is serious and is frequently accompanied by evidence of other organ involvement. This is commonly referred to as HELLP syndrome (Hemolysis Elevated Liver Enzymes and Low Platelets). Some studies stated that up to 20% of women with severe preeclampsia and eclampsia develop HELLP syndrome.[1]

Central nervous system manifestations of preeclampsia and especially the convulsions of eclampsia have been long known. In particular visual symptoms have received much attention. The earliest descriptions of brain involvement came from gross and histological examination, but with modern non-invasive techniques, imaging and Doppler studies have added new insight into cerebrovascular involvement.[1]

The principal postmortem cerebral lesions of severe preeclampsia and eclampsia are edema, hyperemia, focal anaemia, thrombosis and hemorrhage.[1]

The most common abnormalities detected by CT scan are hypodense areas in cerebral cortex which corresponded to the petechial hemorrhages and infarction sites. [1]

Visual disturbances is caused by retinal artery vasospasm or retinal detachment.[1]

Central nervous system manifestations from more widespread cerebral edema are worrisome. In some cases confusion is the major feature. In a few cases overt coma develops. Brain stem herniation is a serious complication for coma patients.[1]

Transcranial Doppler ultrasonography showed increased cerebral perfusion pressure counterbalanced by increased cerebrovascular resistance with no net change in cerebral blood flow.[1]

Compromised placental perfusion from vasospasm is the major factor in the genesis of increased perinatal morbidity and mortality associated with preeclampsia. A study reported that the mean diameter of myometrial spinal

arterioles of normal pregnant women was 500 mm compared to 200 mm in preeclampsia.[1]

Classically in normal pregnancy, spinal arteries are invaded by endovascular trophoblasts. It seems that in preeclampsia decidual vessels but not myometrial vessels are invaded by endovascular trophoblasts. Electron microscopy studies of arteries taken from the uteroplacental implantation site reported endothelial damage, insudation of plasma constituents into vessel walls, proliferation of myointimal cells and medical necrosis. The magnitude of defective trophoblastic invasion of the spiral arteries correlates with the severity of preeclampsia.[1]

1.2.3.5. Pathophysiology of preeclampsia:

20% to 25% of maternal cardiac output supply the uterus and the intervillous space (IVS), allowing exchange of materials between maternal and fetal circulation.[3]

Overall the pressure within this system is low due to anatomic changes in maternal uterine blood vessels. These changes are mediated by extravillous invasive trophoblasts that invade the spiral arteries in the deciduas and upper

third of the myometrium replacing spiral artery endothelium by a fibrinoid extracellular matrix and destroying muscular and elastic elements in the medial tissue. As a result the spiral arteries (now called uteroplacental arteries) become sac like structures unresponsive to maternal vasoconstrictive agents and able to accommodate the blood needed to supply the IVS.[3]

Switching from a proliferative function to an invasive function is essential for normal trophoplastic function, this switch is abnormal in preeclampsia.

The extravillous invasive trophoblasts migrate into the maternal tissue in two waves. During the initial wave (at 6 to 10 weeks), spiral arteries in the deciduas are altered, during the second wave (at 14 to 16 weeks), spiral arteries in the myometrium are altered. In preeclampsia the first invasive wave proceeds normally but there is failure of the second wave.[1]

Several observations support the immunogenetic hypothesis: The higher rate in first pregnancies and lower

rates subsequently. The rate of preeclampsia is increased in pregnancies conceived by a new partner.

Maternal tissues are in direct contact with two trophoblastic tissues: syncytiotrophoblast and extravillous cytotrophoblast, in term of antigenicity both are remarkably inert, containing no classic major histocompatibility (MHC) antigens, extravillous cytotrophoblast does, however, carry a nonclassical truncated MHC/class (1b) antigen known as HLA-G.

Studies suggest that one of the primary functions of HLA-G is inhibition of natural killer cell activity; this would serve to promote trophoblast survival. Some investigators have found that trophoblastic cells from women with preeclampsia fail to express HLA-G mRNA or protein or have attenuated expression of HLA-G.[9]

A familial predisposition to preeclampsia is well established and may operate as a single gene recessive trait. Maternal genotype alone has been implicated because of the increased frequency of preeclampsia in the mothers, daughters and granddaughters of women who have a history

of eclampsia. Another group found that a molecular variant of the angiotensinogen gene (T235) known to be associated with essential hypertension, is also associated with preeclampsia. [1,9]

An autoimmune connection to preeclampsia also is also suspected, as Antiphospholipid syndrome, is associated with particularly high rates of preeclampsia.[1,9]

The underlying abnormality in preeclampsia involves increased vascular sensitivity to pressor hormones and eicosanoids and general arterial constriction. In turn, increased vasoconstriction results in increased blood flow resistance and arterial hypertension.[1,9]

Much investigation has focused on a role for vasoactive eicosanoids. Preeclampsia is marked by deficient prostacyclin (PGI_2) activity and thromboxane A_2 (TXA_2) dominance. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation. Thromboxane A2 is a potent vasoconstrictor and promoter of platelet aggregation.[1,3,8,9]

Candidate circulating factors that damage or activate the endothelium include tumor necrosis factor-α (TNF-α) interleukin-1 (IL-1), endothelin, endothelial growth factor and platelet derived growth factor (PDGF). All these factors are high in sera of preeclamptic woman. [1,3,9]

Coagulopathy may be one of the primary events in the disease. Thrombocytopenia, increased levels of thrombin-antithrombin III complexes, decreased levels of protein C and antithrobmin III and increased levels of fibrin degradation products support the coagulopathy theory. [1,9]

Some investigators believe that increased or dysregulated generation of oxygen free radicals with resultant plasma lipid peroxidation may be the underlying cause of endothelial damage and abnormal placental vascularization in preeclampsia.[1,9]

1.2.3.6. Prediction of preeclampsia:

A variety of biochemical and biophysical markers, based primarily on rationale implicated in the pathology and pathophysiology of preeclampsia, have been proposed for the purpose of prediction. Investigators have attempted to

identify early markers of faulty placentation, reduced placental perfusion, endothelium cell dysfunction and activation of coagulation, all these attempts have resulted in testing strategies with low sensitivity for the prediction.[1,9]

Angiotensin II is infused in a stepwise fashion until there is 20 mmHg rise in diastolic blood pressure. Women requiring less than 8 mg/kg/min of angiotensin II have a positive-predictive value of developing preeclampsia of 20 to40 percent. This is quite good when compared with other tests for prediction.[1]

Elevated uric acid levels in maternal blood, presumably due to decreased renal urate excretion, is frequently found in women with preeclampsia. Studies using uric acid measurement as a predictive factor gave variable results.[1]

Alterations in calcium metabolism as well as deficiencies in dietary intake of calcium have been implicated in the pathophysiology of preeclampsia. Hypocalciuria has been identified with preeclampsia, several investigators performed studies to determine if mid

pregnancy urinary calcium levels might predict the development of preeclampsia, some studies showed good results.[1]

Thrombocytopenia and abnormalities of platelets function may be markers for impending preeclampsia. [1,2]

Increased levels of lipid peroxides coupled with decreased activity of anti-oxidants in women with preeclampsia has raised the possibility that markers of oxidative stress might be useful in the prediction possible markers include malondialdehyde lipid peroxidation iron and homocysteine.[9]

Several cytokines, eg. IL-1 and TNF-α are of interest as possible markers for the development of preeclampsia.[1]

1.2.3.7. Prevention:

A variety of strategies have been used in attempt to prevent preeclampsia. Usually these strategies involve manipulation of diet and pharmacological attempts to modify the pathophysiological mechanisms thought to be responsible for the disease.[1]

Dietary manipulations involve salt restriction, calcium supplementation, and fish oil capsules. [1]

Encouraging results were obtained when low dose aspirin was given to pregnant ladies at risk of preeclampsia, this was attributed to selective suppression of thromboxane synthesis. Sera of women with preeclampsia have markedly reduced antioxidant activity. Studies giving antioxidants as vitamin E to women at risk, showed reduced endothelial cell activation suggesting that such therapy might be beneficial in the prevention of the disease.[1]

1.2.3.8. Management of preeclampsia:

The most effective therapy for preeclampsia is delivery of the fetus and placenta.[1,5,8,9] Therefore in pregnancies at or near term in which the cervix is favorable, labour should be induced. Preeclampsia remote from term presents a much more difficult problem.

Patients with mild preeclampsia are not candidate for delivery if the fetus is immature or the cervix is unfavorable for induction. Successful management usually consisting of rest and observation. The goals of therapy in this situation

are to monitor maternal and fetal parameters while allowing time for the fetus to mature and the cervix to ripen.

Delivery is always appropriate therapy for the mother with severe preeclampsia but may pose significant risks to the premature fetus especially for gestational age less than 32 weeks. Maternal morbidity and mortality associated with severe preeclampsia result principally from severe hypertension, eclampsia and the HELLP syndrome. The goal is to lower the blood pressure to a mildly hypertensive level (diastolic pressure between 90 and 100 mmHg).[1,9] Hydralazine is the preferred agent because of its effectiveness and safety. [1,9]

Eclampsia seizures are a dreaded complication because they are associated with unacceptably high mortality and morbidity rates. Magnesium sulfate the drug of choice for the prevention of eclampsia. It is recommended that all preeclampsia women even those with mild disease be treated with magnesium sulfate for seizure prophylaxis during labour and for the first 24 hours post partum. Delivery of the baby and placenta is the absolute treatment.

Induction of labour is established as soon as it is safe. Nevertheless delivery by cesarean section is the common practice.[9]

1.2.3.9. Prognosis:

Preeclampsia resolves promptly after the delivery of the fetus and placenta. . Hypertension occasionally remains severe and difficult to control after delivery. In this situation methyledopa or any agent can be used, the blood pressure is monitored every week to make sure that the hypertension does not persist. [9]

In primigravidas with mild form of preeclampsia, the disease usually doesn't recur in subsequent pregnancies. With severe preeclampsia the recurrence rate is 30% to 50%. Most multiparus women who have had preeclampsia or eclampsia on top of chronic hypertension have a 70% recurrence rate.[9]

1.2.4. Uric acid tests:

1.2.4.1. Definition:

Uric acid tests are tests that are done to measure the level of uric acid in blood serum or in urine.[10]

1.2.4.2. Purpose:

The uric acid tests are used to evaluate the blood levels of uric acid for gout and to assess uric acid levels in the urine for kidney stone formation. The urine test is used most often to monitor patients already diagnosed with kidney stones, but it can also be used to detect disorders that affect the body's production of uric acid and to help measure the level of kidney functioning.

Uric acid is a waste product that results from the breakdown of purine, a nucleic acid (nucleic acids are the building blocks of DNA.) Uric acid is made in the liver and excreted by the kidneys. If the liver produces too much uric acid or the kidneys excrete too little, the patient will have too much uric acid in the blood. This condition is called hyperuricemia. Supersaturated uric acid in the urine (uricosuria) can crystallize to form kidney stones that may

block the tubes that lead from the kidneys to the bladder (the ureters).[10]

1.2.4.3. Precautions:

- **Blood test:** Patients scheduled for a blood test for uric acid should be checked for the following medications: loop diuretics (Diamox, Bumex, Edecrin, or Lasix); ethambutol (Myambutol); vincristine (Oncovin); pyrazinamide (Tebrazid); thiazide diuretics (Naturetin, Hydrex, Diuril, Esidrix, HydroDiuril, Aquatensen, Renese, Diurese); aspirin (low doses); acetaminophen (Tyienol); ascorbic acid (vitamin C preparations); levodopa (Larodopa); or phenacetin. These drugs can affect test results. Certain foods that are high in purine may increase the patient's levels of uric acid. These include kidneys, liver, sweetbreads, sardines, anchovies, and meat extracts.
- **Urine test:** Patients should be checked for the following medications before the urine test: diuretics, aspirin, pyrazinamide (Tebrazid), phenylbutazone, probenecid (Benemid), and allopurinol (Lopurin). If the patient needs to continue taking these medications, the laboratory

should be notified. The laboratory should also be notified if the patient has had recent x-ray tests requiring contrast dyes. These chemicals increase uric acid levels in urine and decrease them in blood.

1.2.4.4. Description:

The uric acid blood test is performed on a sample of the patient's blood, withdrawn from a vein into a vacuum tube. . The urine test requires the patient to collect all urine voided over a 24-hour period, with the exception of the very first specimen. The patient keeps the specimen container on ice or in the refrigerator during the collection period.

For the blood sample, the patient should be fasting for at least eight hours before the test. The urine test requires a 24-hour urine collection. The urine test does not require the patient to fast or cut down on fluids. Some laboratories encourage patients to drink plenty of fluids during the collection period.

1.2.4.6 Normal results:

Reference values for blood uric acid vary from laboratory to laboratory but are generally found within the

following range: Male: 3.5-7.2 mg/dL; female: 2.6-6.0 mg/dL. Values may be slightly higher in the elderly.

Reference values for 24-hour urinary uric acid vary from laboratory to laboratory but are generally found within the following range: 250-750 mg/24 hours[10].

1.2.4.8. Abnormal results:

The critical value for the blood test is a level of uric acid higher than 12 milligrams per deciliter. Increased production of uric acid may result from eating foods that are high in purine. Increased uric acid levels due to overproduction may also be caused by gout, by a genetic disorder of purine metabolism, or by metastatic cancer, destruction of red blood cells, leukemia, or cancer chemotherapy.

Decreased excretion of uric acid is seen in chronic kidney disease, hypothyroidism, toxemia of pregnancy, and alcoholism. Patients with gout excrete less than half the uric acid in their blood as other persons. Only 10-15% of the total cases of hyperuricemia, however, are caused by gout.

Abnormally low uric acid levels may indicate that the patient is taking allopurinol or probenecid for treatment of gout; may be pregnant; or suffers from Wilson's disease or Fanconi's syndrome.[10]

1.2.5. Background Studies:

Tomoko and Katsugushin, from Jikei University School of Medicine, Japan, studied the changes of serum uric acid levels (SUA) during normal pregnancy, 10 pregnant women studied and their urate metabolism, renal function and hormonal changes were evaluated. They found that (SUA) was low from the onset of pregnancy to the early phase of late pregnancy. (SUA) increased 4 weeks before the deliveries and continued to increase after that, but remain within the normal range. The production of uric acid reflected by urinary uric acid excretion did not change significantly through pregnancy and post partum stages.

Urate clearance changed within the normal range all through the course and did not show significant changes. Creatinine clearance increased and remained above 100 ml/min during pregnancy.

They concluded that two principle resetting are involved in the changes in SUA during normal pregnancy: decrease of SUA at the early phase of pregnancy because of a new balance of renal function caused by the changes of hormones that maintain pregnancy. Slight increases of SUA can be explained by increased production of uric acid which exceeds the dilution due to enlarged circulating volume, a decreasing factor of SUA.[11]

TThe first report of increased uric acid in preeclampsia was by Slemons and Bogerts in 1917.[12]

Hill LM from Mayo clinic studied the metabolism of uric acid in normal pregnancy and toxemic pregnancy, he stated that fluctuations in serum uric acid may be as high as 40% over a 24-hour period; a single value must be evaluated with caution.

He concluded that alterations in the renal handling of uric acid are responsible for the pronounced decrease in serum uric acid over the first 20 weeks of gestation, its gradual increase in the latter part of pregnancy, and its further increase with pregnancy induced hypertension.

Although there is a fair degree of overlap between a normotensive control and a preeclamptic groups, the level of serum uric acid generally correlates with the severity of preeclampsia.[12]

The study conducted by M. Roberts and other at the University of Pittsburgh Medical Centre in Pennsylvania is one of the most important concerning uric acid in preeclampsia. They stated that uric acid is one of the most consistent and earliest detectable changes in preeclampsia and could be a better predictor of fetal risk than blood pressure. [13]

The investigators examined fetal outcome data from 972 pregnancies collected from 1997 to 2000 in a nested case-control study. The participants were nulliparous and had no medical complications pregnancies were grouped in eight categories based on the presence or absence of combinations of hypertension, hyperuricaemia and proteinurea. [13]

In women with gestational hypertension, hyper-uricaemia was associated with shorter gestations, smaller

birth weight centile and increased risk of preterm birth and small-for-gestational age infants. Hyperuricaemia was associated with increased risk of these outcomes in the presence or absence of proteinuria. Authors concluded that hyperuricaemia is at least as effective as proteinurea at identifying gestational hypertensive pregnancies at increased risk. [13]

Ecker, Jeffery et al., measured uric acid levels in blood samples from 344 pregnant women including some with transient hypertension, chronic hypertension, preeclampsia and chronic hypertension and eclampsia. Uric acid levels were higher in those with hypertension than those with normal blood pressure. Women with chronic hypertension and uric acid level of 5.5 mg/dl were 2.5 times more likely to develop preeclampsia.[14]

Bain Bridge SA and Roberts FM (USA) stated that hyperuricaemia is a common finding in preeclamptic pregnancies evident from early pregnancy. Despite the fact that elevated uric acid often pre-dates the onset of clinical

manifestations of preeclampsia, hyperuricaemia is usually considered secondary to altered kidney function.

Hyperuricaemia is associated with adverse fetal outcome in hypertensive pregnancies. They hypothesize that an elevated concentration of uric acid in preeclamptic women is not simply a marker of disease severity but rather contributes directly to the pathogenesis of the disorder. Uric acid ability to promote inflammation, oxidative stress and endothelial dysfunction affects greatly utersplacental dysfunction in preeclampsia.(14)

A study done by Roger A Australia supported strongly the work of Ben Bridge and Roberts as it concluded that rise is serum uric acid in patients with preeclampsia is secondary to placental damage rather than altercating in renal function.(15)

Bakheit KH (Sudan) studied serum uric acid in patients of preeclampsia compared to control group be found that the rising level of serum uric acid correlates well with the severity of hypertension(19).

Wakwe VC and Abudu O (Nigeria) studied 59 women attending antenatal care clinic by measuring plasma uric acid and creatinine clearance. Results confirmed that serum uric acid was able to differentiate between normal pregnancy and PIH at $P < 0.002$. A further rise in serum uric acid in patients of preeclampsia can also predict eclampsia. [20]

Redman and Bale C (South Africa) studied plasma urate and BP in 332 pregnant women with hypertension perinatal mortality was markedly increased when maternal plasma urate was raised. They found that maternal hypertension even severe without hyperurcaemia was associated with an excellent prognosis for the fetus. Conversely when maternal hypertension was mild and hyperuricaemia was severe prognosis for the fetus was poor. They concluded that in term of fetal death serum urate may be more important than blood pressure. [21]

Fadil HE, Northship (USA) studied 17 preclampic women, 22 hypertensive and 13 normal pregnant women all in the 3rd trimester. Results showed that serum uric acid is

elevated, creatinine clearance is impaired and lactate was low in preeclampsia than in control group. [22]

1.3. JUSTIFICATIONS

1. Preeclampsia is a common problem worldwide and Sudan is no exception. So understanding pathogenesis and early diagnosis is essential.
2. Serum uric acid has been reported to be useful in the diagnosis of the disease and may reflect the severity of the condition.

1.4. OBJECTIVES

1.4.1. General objective:

To measure serum uric acid level in preeclamptic women and that of healthy pregnant women in Sudan.

1.4.2. Specific objectives:

1. To measure the serum uric acid level in patients of preeclampsia.
2. To measure serum uric acid level in healthy pregnant Sudanese women.
3. To detect if there is any significant difference.
4. To relate serum uric acid results to the severity of hypertension .

CHAPTER TWO

2- MATERIALS AND METHODS

2.1 Study design:

This is a case control hospital – based, cross-sectional study .

2.2 Study area and duration:

This study was conducted at obstetrics and gynecological department at Khartoum Teaching Hospital.

Duration of the study was five months. (Sept 2009 – Jan 2010)

2.3 Study population:

Pre-eclamptic patients and healthy pregnant women coming from different areas of the Khartoum State.

Inclusion criteria:

1- Pregnant women

2- Gestational age $\geq$ 28 weeks

3- Patient diagnosed as preeclampsia based on BP $\geq$ 140 /90 urine protein $\geq$ ++ dipstick.

Exclusion criteria:

The following are excluded :

1- known hypertensive before

2- known diabetic

3- known renal disease patients.

4- known gout patients .

5- Those who received chemotherapy within 4 weeks.

6- Those on thiazide diuretics .

Matching: case and control groups are matched in age, gravidity and gestational age .

2.4 Sampling:

2.4.1 Case definition:

Women with preeclampsia attending the obstetrics department and who accepted to be included in the study.

Control group: Healthy pregnant women who attended the obstetrics department and who accepted to be included in the study.

2.4.2 Sample size :

Fifty patients with preeclampsi and 50 healthy pregnant women serving as control group were investigated in this study and the sample size was determined according to the availability of resources.

2.4.3 Ethical considerations:

Verbal consents from both control and patients were obtained after explanation of the purpose of the study .

2.5 Data Collection Techniques:

2.5.1 Clinical evaluation:

2.5.1.1 Clinical history and questionnaire*:*

The questionnaire (appendix I) addresses personal data of the patient such as name, age, residence, as well as clinical information as gravity, gestational age and symptoms of preeclampsia.

2.5.1.2 Physical examinations:

Every patient and control were subjected to physical examination which included measuring blood pressure, assessment of lower limb eodema and fundal level.

2.5.2 Blood Sample collection:

From each preeclamptic patient 5 mls of venous blood were collected under aseptic conditions into a disposable syring. Blood immediately delivered into a plain container allowed to completely clot (about 20 minutes) before being centrifuged .

Samples were centrifuged for 2 -3 minutes . 2 mls of serum were pipetted into the sample container of the auto – analyzer, identification of samples was checked throughout analytical steps.

The same steps were applied for the control group.

2.6 Principle of Methods:

Automatic analyzer used: COBAS INTEGRA 400 plus , a product of Roche diagnostics .

2.6.1 Product specifications:

2.6.1.1 System principle:

Random and continuous access, sample selective instrument.

2.6.1.2 Measurement principles:

- Absorbance photometry.
- Fluorescence polarimetry.
- Turbidimetry.
- Potentiometry .

2.6.2 Measurement principle of serum uric acid by COBAS INTEGRA:

Serum uric acid is measured by the absorbance photometer module of the autoanalyzer with the following properties:

- Spectrophotometer grating monochromator and diode array.
- Wavelength range 240 – 800 nm, 12 wavelengths.
- Mono-and bichromatic measurement.
- Light source: Halogen lamps, 100 W.

Analytical method of uric acid:

Common techniques for measuring uric acid in body fluids include:phosphotungstic acid (PTA),uricase and HPLC based methods.

The uricase method is the reference method. Uricase is used either as a single step or as the initial step to oxidize uric acid. Uricase acts on uric acid to produce allantoin, hydrogen peroxide and carbon dioxide. The decrease in absorbance as urate is converted is measured with a spectrometer at 293 nm. Most current enzymatic assays for uric acid involve a peroxidase system coupled with oxygen acceptor to produce a chromogen. The difference in absorbance before and after incubation with uricase is proportional to the uric acid concentration.[23]

2.6.3 Calibration:

The calibration function is the relation between instrument signal (y) and concentration of analyte (X) i.e. y = f (X). This relationship is established by measurement of samples with known amounts of analyte (calibrators).

The only requirement for calibration is that there should be a monotonic relationship between signal and analyte concentration over the analytical measurement range. Otherwise the possibility of error occurs.

In modern automated autoanalyzer COBAS is not exception. The relationship between analytic concentration and signal is often very stable so that calibration is infrequent (e.g. at intervals of several months). Calibration may be needed before the allowed time e.g. when quality control samples is out of the expected range. [23]

2.7 Quality Control:

All patients and controls were interviewed and examined by the reseacher. All tests were run into the analyzer by the same operator.

2.7.1 Quality control of the Auto-analyzer:

COBAS INTEGRA 400 plus Quality Control (QC) function supports established control rules that can be customized to satisfy both local and national QC requirements.

It supports all test groups including routine chemistries, specific proteins, Therapeutic Drug Monitoring (TDM), Drugs of Abuse (DAT), thyroids, and electrolytes. There are three control modes, each with its own set of rules. Each test can have up to six controls at one time. Only the first three can be used as precision controls.

Three modes are recognized: Accuracy, precision, and limit. Each is characterized by one or more rules; when the rule is broken, a flag is generated on the control result. *Precision:* Checks whether control results have violated rules according to the hewhard procedure (commonly known as the Westgard rules) or the Rili-RAK precision rules. Depending on the rules violated, a systematic or random error may have been generated.

Accuracy: Checks whether control results are within a range defined by the assigned value of an assay control and a permissible deviation. When control results are out of range, a systematic error may have been generate. *Limit:* Checks whether control results have exceeded either upper or lower limits. This mode is particularly designed for DAT [16].

2.8 Data Analysis:

Data obtained from the questionnaire was summarized on master sheet. The age, gravidity, blood pressure and serum uric acid level of all studied population were checked.

Preeclamptic patients were categorized into five age groups, eight gravidity groups and four blood pressure groups. Healthy controls were categorized into five age groups ,eight gravidity groups, blood pressure of control group is 120/80.The mean serum uric acid of both case and control groups were calculated. The degree of correlation (coefficient (r-test) and the probability test (p-value) were calculated to show whether there is significance in the relationship between blood pressure and mean serum uric acid level.

Microsoft Excel (Windows 2003, Stata 6.0 for Windows 98/95/NT and Statistical Package of Social Sciences (SPSS) version 16 were used for data analysis.

CHAPTER THREE

3- RESULTS

A total number of fifty Sudanese preeclamptic and fifty healthy pregnant women matched in age, gestational age and gravity were recruited to this study.

Both patients and controls were not known to be hypertensive ,diabetic, or patients of renal disease, did not received chemotherapy or thiazid dieuretics within 4 weeks of the study.

The studied population was divided into 5 age groups as follows:

Eight women (8%) between 21-25 yrs, 22 women (22%), between 26-30 yrs, 16 women (16%) between 31 - 35 yrs and 23 women (23 %) between 36 - 40 years old.

The studied cases age distribution was as follows:

Five women (16%)) less than 21 yrs, 17 women (34%), between 21- 25 yrs, 7 women (14%) between 26-30 yrs, 9 women (18%) between 31- 35 yrs and 12 women (24%)

between 36 - 40 years old. (Table 1)

The healthy controls age distribution was as follows:

Three women (6%) < 21 years, 14 women (28%) between 21-25 yrs, 15 women (30%), between 26-30 yrs, 7 women (14%) between 31 - 35 yrs and 11 women (22%) between 36 - 40 years old. (Table 2)

The gravidity distribution of the studied population was as follows:

Thirty eight women (38%) primigravida,-25 women (25%) gravida 2, 16 women (16%), 7 women (7%) gravida 4, 5 women (5%) gravida 5, 4 women (4%) gravida 6, 4 women (4%) gravida 7, and 1 woman (1%) gravida 8. (Table 3)

Case group distribution according to gravidity was as follows:

Fourteen women (48%) primigravida, 11 women (25%) gravida 2, 8 women (16%) gravida 3,2 women (4%) gravid 4, 1 woman (2%) gravida 5, 3 women (6%) gravida 6 and 1 woman (2%) gravida 8. (Table 4)

Distribution of control group according to gravidity was as follows:

Twenty eight women (48%) primigravida, 14 women (28%) gravida 2, 8 women (16%) gravida 3, 5 women (10%) gravid 4, 4 women (8%) gravida 5, 1 woman (2%) gravida 6 and 4 women (8%) gravid 7.

Distribution of case groups according to blood pressure was as follows:

Nineteen women (38%) were 140/90 mmHg, 3 women (6%) 140/100 . mmHg, 16 (32%) were 150/100 mmHg and 12 women (24%) were *160/110* mmHg.

The control group were normotensive i.e 120/80 mmHg.

Mean serum uric acid level was calculated:

Case: 50 women; the mean serum uric acid was 7.35 mg/dL.

Control: 50 women; the mean was 4.47 mg/dL.

The mean serum uric acid of both case and control was 5.91 mg/dL. (Table 5)

Serum uric acid of case gravidity groups was calculated:

Twenty four women were primigravia; their mean uric acid 7.68 mg/dL, 11 women were gravida II; their mean uric acid 6.79 mg/dL, 8 women were gravida III; their mean uric acid is 6.95 mg/dL, 2 women were gravida IV; their mean uric acid is 7.20 mg/dL, only 1 woman was gravida V; her serum uric acid is 6.60 mg/dL, 3 women were gravid VI; their mean uric acid 7.76 mg/dL and one woman were gravida VIII; their mean uric acid 6.60 mg/dL.

The mean of all cases were 7.35 mg/dl (Table 6)

The relation between the gravidity and serum uric acid in preeclampsia; P value = .458 is statistically not significant.

Mean serum uric acid of control gravidity groups was calculated:

Fourteen women were primigravias; their mean uric acid is 4.38 mg/dL, 14 women were gravid II, their mean uric acid 4.55 mg/dL, 8 women were gravida III; their mean uric acid is 4.36 mg/dL, 5 women were gravida IV; their

mean uric acid is 4.40 mg/dL, 4 women were gravida V; their mean uric acid is 4.70 mg/dL, only one woman was gravida VI; her serum uric acid is 5.00 mg/dL and 4 women were gravida VII; their mean uric acid 4.42 mg/dL.

The mean of all cases were 4.47 mg/dL. (Table 7).

Patients of preeclampsia were put into four groups of blood pressure and the mean serum uric acid of each group was as follows:

Nineteen women (38%) were 140/90 mmHg, their mean serum uric acid was 6.45 mg/dL. 3 women (6%) of blood pressure 140/100 mmHg. Their mean serum uric acid was 6.85 mg/dL. 16 women (32%) of blood pressure 150/100 mmHg; their mean serum uric acid was 7.75 mg/dL. and 12 women (24%) of blood pressure 160/100 mmHg; their mean serum uric acid was 8.35 mg/dL. (Figure 1, Table 8).

Statistically probability value and correlation coefficient test were calculated to show whether there is significance in relationship between blood pressure and serum uric acid lvel, they proved to be highly significant. P value = 0.000. r value 0.6.

Table 1: Age distribution of case group

Age (Years)	Frequency	Percentage (%)
< 21	5	10.0
21- 25	17	34
26 - 30	7	14
31 - 35	9	18.0
36 - 40	12	24
Total	**50**	**100.0**

Table (2): Age distribution of control group (n = 50)

Age (Years)	Frequency	Percentage (%)
> 21	3	6.0
21- 25	14	28.0
26 - 30	15	30
31 - 35	7	14
36 - 40	11	22
Total	**50**	**100.0**

Table (3): Gravity distribution of case and control

(n = 100)

Gravidity	Frequency	Percentage (%)
PG	38	38.0
II	25	25.0
III	16	16.0
IV	7	7.0
V	5	5.0
VI	4	4.0
VII	4	4.0
VIII	1	1.0
Total	**100**	**100.0**

Table (4): Gravidity distribution of case group

	Frequency	**Percentage (%)**
PG	24	48.0
II	11	22.0
III	8	16.0
IV	2	4.0
V	1	2.0
VI	3	6.0
VIII	1	2.0
Total	**50**	**100.0**

Table (5): Serum uric acid of control & case group

Group	n	**Mean** ***mg/dL***
Case	50	7.35
Control	50	4.47

Table (6): Serum uric acid of case group

(n = 50)

Gravidity (the number of Pregnancy)	**Frequency**	**Mean mg/dL**
PG	24	7.68
II	11	6.97
III	8	6.95
IV	2	7.20
V	1	6.6
VI	3	7.8
VIII	1	6.6

P value = .458 is not significant

Table (7): Serum uric acid of control group

(n = 50)

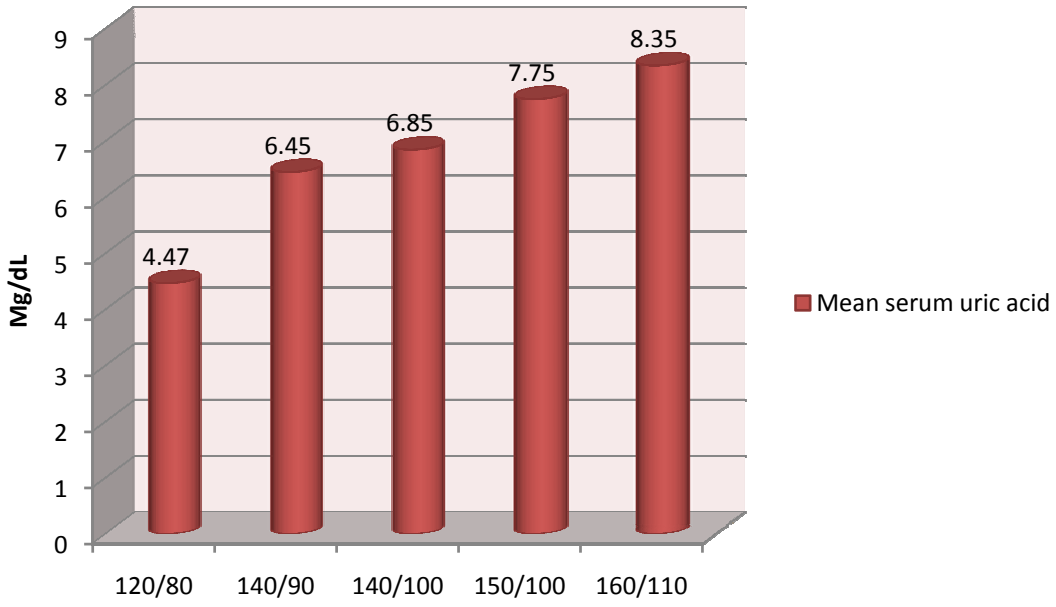
Gravidity (the number of pregnancy)	Frequency	Mean mg/dL
PG	14	4.38
II	14	4.55
III	8	4.36
IV	5	4.40
V	4	4.70
VI	1	5.00
VII	4	4.42

Table (8): Mean serum uric acid of case group blood pressure.

Blood pressure mmHg	Frequency	Mean serum uric acid (mg/dL)
140/90	19	6.45
140/100	3	6.85
150/100	16	7.75
160/110	12	8.35
Total	**50**	

P value = 0.000 is significant
r test = 0.6 is significant

Figure: Mean serum uric acid compared with blood pressure



CHAPTER FOUR

4- DISCUSSION

The study covered 100 patients 50 case/50 control.

The study has not considered: residence, tribe, education and socio-economic status in the analysis, as these factors are more useful in bigger community-based studies.

The age group studied was 20-40 years old, as this age is accepted worldwide as safe for conception and most preeclampsia incidence is associated with extremities of maternal age.

The study showed greater number of preeclampsia around early twenties late thirties and forty this result support studies linking extremities of maternal age with preeclampsia[1,9].

The biggest number of pregnancies was primigravidus for both cases and controls 38%, 5% gravida II, 16% gravida

III, 7% gravida IV, 5% gravida V, 4% gravida 6, 4% gravida VII and only one percent gravida VIII.

This declining percent with greater number of pregnancies may show a tendency of having less children or that people prefer family planning.

Of the high percent of primagravida (38%) women, preeclamptic primagravidus were more than healthy primigravidus (24 versus 14) this finding is in consistence with the studies putting primagravidus as a risk factor [1,5,8,9]

There is no relationship between gravidity and serum uric acid i.e increased parity is not associated with rise in serum uric acid as far as we know no one linked greater gravity with the rise in serum uric acid.

Serum uric acid of the control group of a mean 4.47 mg/dL is within the normal range (2.6 – 6 mg/dL). This is compatible with the scientific fact that normal pregnancy is not associated with rise in serum uric acid[1,9].

Serum uric acid of the case group of a mean of 7.35 mg/dL is higher than the normal range this is

consistent with the results of M Roberts and others in Pennsylvania, one of the most important studies about the rise of serum uric acid with preeclampsia that study cover 972 case of preeclampsia and the mean serum uric acid 7.6 mg/dL this is close to our results[13].

Ecker and Jeffry et al on their study titled clinical utility of serum uric acid measurement in hypertensive disease of pregnancy found that precelamptic women with serum uric acid of 6.5 mg/dL are 2.5 times more likely to develop preeclmpsia[14].

Tsukimori, Yoshitomi, et al Japan (2008) in their study that aim to investigate whether serum uric acid level correlate with superoxide generation and oxidative stress in preeclampsia[17]. They found that the mean serum uric acid is 6.6 $\pm$ 1.5 mg/dL in preeclampsia compared to normal pregnancy of 4.0 $\pm$ 0.7 mg/dL. This is also close to our control and case groups values.

S Thangaratinam, Ismail, et al, UK (2006); in their study about accuracy of serum uric acid in predicting complications of preeclampsia. Found that serum uric acid

greater than or equal to 7.25 mg/dL is highly predictive of eclampsia. This value is no far from our findings[18].

Dividing the high blood pressure into 4 groups (Table 8) and relating blood pressure to serum uric acid (Figure 1) showed that the higher the Blood pressure the higher the level of serum uric acid.

Probability test done supported this strongly (P = 0.000). The relation between the rise in BP and uric acid was in consistence with the work done by Eker, Jeffry et aI[14].

Finally Bakheit KH (Sudan) studied serum uric acid in preeclampsia compared to control found that the mean serum uric acid of control 4.5 mg/dL and that of case group 6.5 mg/dL; these values are approximate to the results of this study .

4.1 CONCLUSION

According to the results obtained and the discussion; conclusions are:

1. Preeclampsia is associated with rise in serum uric acid level.
2. The higher the blood pressure in preeclampsia the higher the rise in serum uric acid level.
3. Hyperuricaemia in preeclampsia is common in primigravidus status.
4. Increased gravidity is not associated with hyperuricaemia.

4.1 RECOMMENDATIONS

1. Serum uric acid measurement should be included in the follow up of preeclampsia.
2. Serum uric acid level can be a good predictive factor for preeclampsia.
3. Further studies about uric acid in preeclampsia should be conducted.

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Questionnaire

SERUM URIC ACID IN PATIENTS WITH PREECLAMPSIA COMPARED TO CONTROL

Serial No:……. Date: ……..

1. Name:…….
2. Age: ……..
3. Residence:……
4. Gravidity:…….
5. Gestational Age:……
6. Symptoms and history of present disease: ……..
7. Physical examination:
    a. BP
    b. Oedema
8. Results of investigations:
    a. Proteinuria
    b. Serum uric acid